PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 02 April 2002 (02.04.02)	
International application No. PCT/US00/18817	**Applicant's or agent's file reference** 61765.00003
International filing date (day/month/year) 11 July 2000 (11.07.00)	**Priority date** (day/month/year) 12 July 1999 (12.07.99)
Applicant KAWANISHI, Masashi et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 December 2000 (18.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer François BAECHLER
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Int'l Unis Bpc PCT/US00/18817

PATENT COOPERATION TREATY

+ Article 19 Amend due 12-12-00

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

WOLFFE, Susan, A.
Banner & Witcoff, Ltd.
Eleventh floor
1001 G Street, N.W.
Washington, DC 20001-4597
ETATS-UNIS D'AMERIQUE

RECEIVED
NOV - 1 2000
BANNER & WITCOFF, LTD.

MH Date 11/1/00

Date of mailing (day/month/year) 27 October 2000 (27.10.00)	
Applicant's or agent's file reference 61765.00003	**IMPORTANT NOTIFICATION**
International application No. PCT/US00/18817	International filing date (day/month/year) 11 July 2000 (11.07.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 12 July 1999 (12.07.99)
Applicant G.D. SEARLE & CO. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
12 July 1999 (12.07.99)	60/142,956	US	18 Sept 2000 (18.09.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Magda BOUACHA M.B

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

Intl

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
WOLFFE, Susan, A.
Banner & Witcoff, Ltd.
Eleventh floor
1001 G Street, N.W.
Washington, DC 20001-4597
ETATS-UNIS D'AMERIQUE

61765.00003

RECEIVED
JAN 2001
BANNER & WITCOFF LTD.

National Phase Due 1/12/02

Date of mailing (day/month/year) 18 January 2001 (18.01.01)	
Applicant's or agent's file reference 61765.00003	**IMPORTANT NOTICE**
International application No. PCT/US00/18817	**International filing date** (day/month/year) 11 July 2000 (11.07.00)
Priority date (day/month/year) 12 July 1999 (12.07.99)	
Applicant G.D. SEARLE & CO. et al	

MH Due 1/30/01

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,BZ,KP,KR,MZ,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,
   GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,
   NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   18 January 2001 (18.01.01) under No. WO 01/03697

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO **34, chemin d s Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PCT/US00/18817

DHH/SAW

JMP

PATENT COOPERATION TREATY

Int'l

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

61765.00003

WOLFFE, Susan, A.
Banner & Witcoff, Ltd.
Eleventh floor
1001 G Street, N.W.
Washington, DC 20001-4597
ETATS-UNIS D'AMERIQUE

NOV - 1 2001

BANNER & WITCOFF LTD.

National Phase Ext. 12JA2002

Date of mailing (day/month/year)	
19 October 2001 (19.10.01)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
61765.00003	
International application No.	**International filing date** (day/month/year)
PCT/US00/18817	11 July 2000 (11.07.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
ASAHI CHEMICAL INDUSTRY CO., LTD. 632-1, Mifuku, Ohito-cho Tagata-gun Shizuoka-ken 410-2321 Japan	JP	JP
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
ASAHI KASEI KOGYO KABAHIKI KAISHA' 632-1, Mifuku, Ohito-cho Tagata-gun Shizuoka-ken 410-2321 Japan	JP	JP
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Beate GIFFO-SCHMITT
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

004386606

Int'l

NT COOPERATION TREA

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SUSAN A. WOLFFE
BANNER & WITCOFF, LTD.
1001 G STREET, N.W.
ELEVENTH FLOOR
WASHINGTON DC 20001-4597

PCT

NOTIFICATION OF RECEIPT
OF DEMAND BY COMPETENT INTERNATIONAL
PRELIMINARY EXAMINING AUTHORITY

(PCT Rule 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing *(day/month/year)*	03 APR 2001
Applicant's or agent's file reference: 61765.00003	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/18817	11 JUL 00	12 JUL 99

Applicant: G.D. SEARLE & CO.

1. The applicant is hereby **notified** that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

   19 December 00 (19.12.00)

   61765.00003
   RECEIVED
   APR 04 2001
   BANNER & WITCOFF LTD.

2. That date of receipt is:

   ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).

   ☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).

   ☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION**: That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

   ☐ *(If applicable)* This notification confirms the information given by telephone, facsimile transmission or in person on: _____

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/US	Authorized officer
Assistant Commissioner for Patents Box PCT Washington, D.C. 20231 Attn: IPEA/US Facsimile No.	Telephone No.

Form PCT/IPEA/402 (July 1998)

A[illegible]NT COOPERATION TRE[illegible]

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

OCT 1 0 2000

To:

WOLFFE, Susan, A.
Banner & Witcoff, Ltd.
Eleventh floor
1001 G Street, N.W.
Washington, DC 20001-4597
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
21 September 2000 (21.09.00)	
Applicant's or agent's file reference	**International application No.**
61765.00003	PCT/US00/18817

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

G.D. SEARLE & CO. et al (for all designated States except US)
KAWANISHI, Masashi et al (for US)

International filing date	:	11 July 2000 (11.07.00)
Priority date(s) claimed	:	12 July 1999 (12.07.99)
Date of receipt of the record copy by the International Bureau	:	11 August 2000 (11.08.00)
List of designated Offices	:	

AP :GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
National :AE,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,US,UZ,VN,YU,ZA,ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

[X] time limits for entry into the national phase

[X] confirmation of precautionary designations

[X] requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
David Lopez-Ramirez

Telephone No. (41-22) 338.83.38

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

Int'l

PATENT COOPERATION TREATY

JAN 29 2001

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT BANNER & WITCOFF LTD.

To:
WOLFFE, Susan A. et al
BANNER & WITCOFF, LTD.
1001 G Street, N.W.
Eleventh Floor
Washington, DC 20001-4597
ETATS-UNIS D'AMERIQUE

Fax: (202) 508-9299

ONLY BY FASCIMILE

NOTIFICATION OF TRANSMITTAL OF DEMAND TO THE INTERNATIONAL BUREAU OR TO THE COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rule 59.3(a) and (f) and Administrative Instructions, Section 601(b))

Date of mailing *(day/month/year)*	29.01.01
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
61765.00003	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 00/18817	11/07/2000	12/07/1999

Applicant
G.D. SEARLE & CO. et al

1. This International Preliminary Examining Authority, which has received on the date indicated below a demand for international preliminary examination, is not competent for the international preliminary examination of the international application:

18/12/2000 *(date of receipt)*

2. The applicant is hereby notified that:

☐ this Authority has transmitted the demand to the International Bureau which will transmit it, as the case may be, directly to the competent International Preliminary Examining Authority and inform the applicant accordingly, or invite the applicant to indicate the competent International Preliminary Examining Authority to which the demand should be transmitted.

☒ this Authority has transmitted the demand directly to the competent International Preliminary Examining Authority which is: IPEA/US

3. The date of receipt indicated above has been marked on the demand; the demand will, in accordance with Rule 59.3(e), be considered to have been received by the competent International Preliminary Examining Authority on that date of receipt.

☐ ATTENTION: That date of receipt is AFTER the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices)(Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

☐ *(If applicable)* The applicant has already been informed accordingly by telephone, facsimile transmission or in person, on:

_____

4. A copy of this notification is being sent to the International Bureau or to the competent International Preliminary Examining Authority indicated above, as the case may be.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	P. Donnelly. DONNELLY P P Tel. (+49-89) 2399-2362

INTERNATIONAL SEARCH REPORT

Interna[redacted]application No.
PCT/US00/18817

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/536; C07D 265/18
US CL : 514/230.5; 544/92
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/230.5; 544/92

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN/CAS: structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X, P	US 5,985,872 A (ABOOD et al.) 16 November 1999 (16.11.99), entire document.	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 August 2000 (25.08.2000)	12 OCT 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Richard L. Raymond Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

For receiving Office use only

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

International Application No.	
International Filing Date	
Name of receiving Office and "PCT International Application"	

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 61765.00003

Box No. I TITLE OF INVENTION
2-AMINO-BENZOXAZINONES FOR THE TREATMENT OF HERPES SIMPLEX VIRUS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

G.D. SEARLE & CO.
Corporate Patent Department
P.O. Box 5110
Chicago, Illinois 60680-5110
US

[ ] This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No. N/A

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: [ ] all designated States **[X] all designated States except the United States of America** [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ASAHI CHEMICAL INDUSTRY CO., LTD.
632-1, Mifuku, Ohito-Cho
Tagata-Gun, Shizuoka-Ken
410-2321 JAPAN

This person is:

[X] applicant only

[ ] applicant and inventor

[ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: JP

State *(that is, country)* of residence: JP

This person is applicant for the purposes of: [ ] all designated States **[X] all designated States except the United States of America** [ ] the United States of America only [ ] the States indicated in the Supplemental Box

[ ] Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: [X] agent [ ] common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Susan A. Wolffe
BANNER & WITCOFF, LTD.
1001 G Street, N.W.
Eleventh Floor
Washington, D.C. 20001-4597
US

Telephone No. (202) 508-9100

Facsimile No. (202) 508-9299

Teleprinter No. N/A

[ ] **Address for correspond nc** : Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Masashi KAWANISHI
632-1, Mifuku, Ohito-Cho
Tagata-Gun, Shizuoka-Ken
410-2324 JAPAN

This person is:
[ ] applicant only
[ ] applicant and inventor
[X] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: JP

State *(that is, country)* of residence: JP

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America **[X] the United States of America only** [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Wataru TAKAHASHI
632-1, Mifuku, Ohito-Cho
Tagata-Gun, Shizuoka-Ken
410-2324 JAPAN

This person is:
[ ] applicant only
[ ] applicant and inventor
[X] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: JP

State *(that is, country)* of residence: JP

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America **[X] the United States of America only** [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
[ ] applicant only
[ ] applicant and inventor
[ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
[ ] applicant only
[ ] applicant and inventor
[ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: [ ] all designated States [ ] all designated States except the United States of America [ ] the United States of America only [ ] the States indicated in the Supplemental Box

[ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a)*(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

[X] **AP** **ARIPO Patent: GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

[X] **EA** **Eurasian Patent: AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

[X] **EP** **European Patent: AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

[X] **OA** **OAPI Patent: BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

[X] **AE** United Arab Emirates
[X] **AL** Albania .....
[X] **AM** Armenia .....
[X] **AT** Austria .....
[X] **AU** Australia .....
[X] **AZ** Azerbaijan
[X] **BA** Bosnia and Herzegovina .....
[X] **BB** Barbados
[X] **BG** Bulgaria .....
[X] **BR** Brazil .....
[X] **BY** Belarus .....
[X] **BZ** Belize
[X] **CA** Canada
[X] **CH and LI** Switzerland and Liechtenstein
[X] **CN** China .....
[X] **CR** Costa Rica .....
[X] **CU** Cuba .....
[X] **CZ** Czech Republic .....
[X] **DE** Germany .....
[X] **DK** Denmark .....
[X] **DM** Dominica
[X] **EE** Estonia .....
[X] **ES** Spain .....
[X] **FI** Finland .....
[X] **GB** United Kingdom
[X] **GD** Grenada
[X] **GE** Georgia .....
[X] **GH** Ghana .....
[X] **GM** Gambia
[X] **HR** Croatia .....
[X] **HU** Hungary .....
[X] **ID** Indonesia
[X] **IL** Israel .....
[X] **IN** India .....
[X] **IS** Iceland
[X] **JP** Japan .....
[X] **KE** Kenya .....
[X] **KG** Kyrgyzstan .....
[X] **KP** Democratic People's Republic of Korea .....
[X] **KR** Republic of Korea .....
[X] **KZ** Kazakhstan .....
[X] **LC** Saint Lucia
[X] **LK** Sri Lanka
[X] **LR** Liberia
[X] **LS** Lesotho .....
[X] **LT** Lithuania
[X] **LU** Luxembourg
[X] **LV** Latvia
[X] **MA** Morocco .....
[X] **MD** Republic of Moldova .....
[X] **MG** Madagascar .....
[X] **MK** The former Yugoslav Republic of Macedonia .....
[X] **MN** Mongolia
[X] **MW** Malawi .....
[X] **MX** Mexico .....
[X] **MZ** Mozambique .....
[X] **NO** Norway
[X] **NZ** New Zealand .....
[X] **PL** Poland .....
[X] **PT** Portugal .....
[X] **RO** Romania
[X] **RU** Russian Federation .....
[X] **SD** Sudan
[X] **SE** Sweden
[X] **SG** Singapore
[X] **SI** Slovenia .....
[X] **SK** Slovakia .....
[X] **SL** Sierra Leone .....
[X] **TJ** Tajikistan .....
[X] **TM** Turkmenistan .....
[X] **TR** Turkey .....
[X] **TT** Trinidad and Tobago .....
[X] **TZ** United Republic of Tanzania
[X] **UA** Ukraine .....
[X] **UG** Uganda .....
[X] **US** United States of America .....
[X] **UZ** Uzbekistan .....
[X] **VN** Viet Nam .....
[X] **YU** Yugoslavia .....
[X] **ZA** South Africa .....
[X] **ZW** Zimbabwe .....

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

[ ] .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

*1. If, in any of the Boxes, **the space is insufficient** to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient,in particular:*

*(i) **if more than two persons are involved as applicants and/or inventors** and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

*(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication **"the States indicated in the Supplemental Box"** is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

*(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, **the inventor or the inventor/applicant is not inventor for th purposes of all designated States or for the purposes of the United States of America:** in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

*(iv) if, in addition to the agent(s) indicated in Box No. IV, there are **further agents:** in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

*(v) if, in Box No. V, the name of an State (or OAPI) is accompanied by the indication **"patent of addition,"** or **"certificate of addition,"** or if, in Box No. V, the name of the United States of America is accompanied by an indication **"continuati n"** or **"continuation-in-part"**: in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

*(vi) if, in Box No. VI, there are **more than three earlier applications whose priority is claimed:** in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;*

*(vii) if, in Box No. VI, **the earlier application is an ARIPO application:** in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.*

*2. If, with regard to the **precautionary designation statement** contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

*3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning **non-prejudicial disclosures or exceptions to lack of novelty:** in such case write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.*

Continuation of Box No. IV:

ALTHERR, Robert F.
BANNER, Donald W.
BANNER, Pamela I.
BECKET, William W.
FEDEROCHKO, Gary D.
FISHER, William J.
HONG, Patricia E.
HOSCHEIT, Dale H.
JACKSON, Thomas H.
KAGAN, Sarah A.
McKIE, Edward F. Jr.
MEDLOCK, Nina L.
NIEGOWSKI, James A.
PETERSON, Thomas L.
POTENZA, Joseph M.
SKERPON, Joseph M.
SCHAD, Steven P.
WOLFFE, Franklin D.
WOLFFE, Susan A.
WRIGHT, Bradley C.

All members of the firm of BANNER & WITCOFF, LTD. at the address, telephone and telefacsimile numbers as indicated in Box No. IV.

Box No. VI PRIORITY CLAIM [ ] Further priority claims are indicated in the Supplemental Box.

		Where earlier application is:		
Filing date of earlier application (day/month/year)	Number of earlier application	national application: country	regional application:* regional Office	international application: receiving Office
item (1) 12 July 1999	60/142,956	US		
item (2)				
item (3)				

[X] The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection olf Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:
ISA/US

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:
Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	5 sheets
description (excluding sequence listing part)	:	40 sheets
claims	:	6 sheets
abstract	:	1 sheet
drawings	:	0 sheets
sequence listing part of description	:	0 sheets
Total number of sheets	:	52 sheets

This international application is **accompanied by** the item(s) marked below:
1. **[X] fee calculation sheet (duplicate)**
2. [ ] separate signed power of attorney
3. [ ] copy of general power of attorney; reference number, if any:
4. [ ] statement explaining lack of signature
5. [ ] priority document(s) identified in Box No. VI as item(s):
6. [ ] translation of international application into (language):
7. [ ] separate indications concerning deposited microorganism or other biological material
8. [ ] nucleotide and/or amino acid sequence listing in computer readable form
9. **[X] other *(specify)*: Transmittal**

Figure of the drawings which should accompany the abstract: 0

Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Susan A. Wolffe
Agent for the Applicant(s)

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: [ ] received: [ ] not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA/	6. [ ] Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT CHAPTER II
DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 61765.00003
International application No. PCT/US00/18817	International filing date *(day/month/year)* 11 July 2000 (11.07.00)	(Earliest) Priority date (*day/month/year*) 12 July 1999 (12.07.99)

Title of invention: 2-AMINO-BENZOXAZINONES FOR THE TREATMENT OF HERPES SIMPLEX VIRUS

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	Telephone No.:
G.D. SEARLE & CO Corporate Patent Department P.O. Box 5110 Chicago, Illinois 60680-5110 United States of America	Facsimile No.: Teleprinter No.:

State *(that is, country)* of nationality: US	State *(that is, country)* of residence: US

Name and address: *(Family name followed by given name; for legal entity, full official designation. The address must include postal code and name of country.)*

ASAHI CHEMICAL INDUSTRY CO. LTD.
632-1, Mifuku, Ohito-Cho
Tagata-Gun, Shizuoka-Ken
410-2321 JAPAN

State *(that is, country)* of nationality: JP	State *(that is, country)* of residence: JP

Name and address: *(Family name followed by given name; for legal entity, full official designation. The address must include postal code and name of country.)*

Masashi KAWANISHI
632-1, Mifuku, Ohito-Cho
Tageta-Gun, Shizuoka-Ken
410-2324 JAPAN

State *(that is, country)* of nationality: JP	State *(that is, country)* of residence: JP

Further applicants are indicated on a continuation sheet.

International application No.
PCT/US00/18817

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not to be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

TAKAHASHI, Wataru
632-1, Mifuku, Ohito-Cho
Tagata-Gun, Shizuoka-Ken
410-2324 JAPAN

State *(that is, country)* of nationality: JP

State *(that is, country)* of residence: JP

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

Further applicants are indicated on another continuation sheet.

International application No.
PCT/US00/18817

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WOLFFE, Susan A.
BANNER & WITCOFF, LTD.
1001 G Street, N.W.
Eleventh Floor
Washington, D.C. 20001
United States of America

Telephone No.:
(202) 508-9100

Facsimile No.:
(202) 508-9299

Teleprinter No.:
N/A

[ ] **Address for Correspondence**: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination **to start on the basis of:**

   [X] the international application as originally filed

   the description [X] as originally filed
   [ ] as amended under Article 34

   the claims [ ] as originally filed
   [ ] as amended under Article 19 (together with any accompanying statement)
   [ ] as amended under Article 34

   the drawings [ ] as originally filed
   [ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [X] The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired).*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH
[X] which is the language in which the international application was filed.
[ ] which is the language of a translation furnished for the purposes of international search.
[ ] which is the language of publication of the international application.
[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby **elects all eligible States** (*that is, all States which have been designated and which are bound by Chapter II of the PCT*) excluding the following States which the applicant wishes **not to elect:** _____

_____

International application No.
PCT/US00/18817

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only	
			received	not received
1. translation of international application	:	sheets	[ ]	[ ]
2. amendments under Article 34	:	sheets	[ ]	[ ]
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	[ ]	[ ]
4. copy (or, where required, translation) of statement under Article 19	:	sheets	[ ]	[ ]
5. letter	:	sheets	[ ]	[ ]
6. other *(specify)*	:	sheets	[ ]	[ ]

The demand is also accompanied by the item(s) marked below:

1. [X] fee calculation sheet
2. [ ] separate signed power of attorney
3. [ ] copy of general power of attorney; reference number, if any:
4. [ ] statement explaining lack of signature
5. [ ] nucleotide and/or amino acid sequence listing in computer readable form
6. [ ] other *(specify):*

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Susan A. Wolffe
Agent for the Applicant(s)

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. [ ] The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
   [ ] The applicant has been informed accordingly.
4. [ ] The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. [ ] Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

For International Preliminary Examining Authority use only

International application No. PCT/US00/18817	Date stamp of the IPEA
Applicant's or agent's file reference 61765.00003	
Applicant G.D. SEARLE & CO.	

Calculation of prescribed fees

1. Preliminary examination fee ..... EUR 1,533 [P] _____

2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)* ..... EUR 147 [H] _____

3. Total of prescribed fees
   Add the amounts entered at P and H and enter total in the TOTAL box ..... EUR 1,680 TOTAL _____

Mode of Payment

[ ] authorization to charge deposit account with the IPEA (see below)

[ ] cheque

[ ] postal money order

[X] bank draft

[ ] cash

[ ] revenue stamps

[ ] coupons

[ ] other *(specify)*:

Deposit Account Authorization ***(this mode of payment may not be available at all IPEAs)***

The IPEA/ EP [ ] is hereby authorized to charge the total fees indicated above to my deposit account.

[ ] *(this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

N/A	14 December 2000 (14.12.00)	Susan A. Wolffe
Deposit Account Number	Date *(day/month/year)*	Signature: Susan A. Wolffe. Reg. No. 33,568

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organizati n
International Bureau

(43) International Publication Date
18 January 2001 (18.01.2001)

PCT

(10) International Publication Number
WO 01/03697 A1

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(22) International Filing Date: 11 July 2000 (11.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/142,956 12 July 1999 (12.07.1999) US

(71) Applicants *(for all designated States except US)*: **G.D. SEARLE & CO.** [US/US]; Corporate Patent Department, P.O. Box 5110, Chicago, IL 60680-5110 (US). **ASAHI CHEMICAL INDUSTRY CO., LTD.** [JP/JP]; 632-1, Mifuku, Ohito-cho, Tagata-gun, Shizuoka-ken 410-2321 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KAWANISHI, Masashi** [JP/JP]; 632-1 Mifuku, Ohito-cho, Tagata-gun, Shizuoka-ken 410-2324 (JP). **TAKAHASHI, Wataru** [JP/JP]; 632-1, Mifuku, Ohito-cho, Tagata-gun, Shizuoka-ken 410-2324 (JP).

(74) Agents: **WOLFFE, Susan, A.** et al.; Banner & Witcoff, Ltd., Eleventh floor, 1001 G Street, N.W., Washington, DC 20001-4597 (US).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/03697 A1

(54) Title: 2-AMINO-BENZOXAZINONES FOR THE TREATMENT OF HERPES SIMPLEX VIRUS

(57) Abstract: Antiviral agents and methods for treating Herpes Simplex Virus.

2-AMINO-BENZOXAZINONES FOR THE TREATMENT OF HERPES SIMPLEX VIRUS

Field of the Invention

This invention is in the field of antiviral agents and specifically relates to compounds, compositions and methods for treating Herpes Simplex Virus.

Background of the Invention

There is a great need for new therapies for the treatment of viral diseases. Whereas there has been great progress in developing a variety of therapies for the treatment of bacterial infections, there are few viable therapies for the treatment of viruses. Zidovudine is the primary approved treatment for human immunodeficiency virus. Ganciclovir, acyclovir, and foscarnet are currently utilized for the treatment of herpesvirus infections. However, these therapies can have substantial side effects based on their deleterious effects on host cell DNA replication or their effect on a limited number of viral infections. In addition, viruses are known to develop resistance to therapies, which causes a progressive decline in efficacy.

Viruses are classified into broad categories based on whether they incorporate RNA or DNA. Important virus families classified of the DNA type include adenoviridae, poxviridae, papovaviridae and herpesviridae.

Herpesviridae is a family of DNA viruses which include herpes simplex virus type-1 (HSV-1), herpes simplex virus type-2 (HSV-2), cytomegalovirus (CMV), varicella-zoster virus (VZV), Epstein-Barr virus, human herpesvirus-6 (HHV6), human herpesvirus-7 (HHV7), human herpesvirus-8 (HHV8), pseudorabies and rhinotracheitis, among others.

It is known that herpesviruses express their genetic content by directing the synthesis of a number of proteins encoded by the herpesvirus DNA in the host cell. One of the important virus-encoded proteins is made as a precursor consisting of an amino terminal-located protease and carboxyl terminal-located assembly protein. This precursor is proteolytically processed in an autocatalytic manner at a specific

amino acid sequence known as the "release" site yielding separate protease and assembly protein. The assembly protein is cleaved further by the protease at another specific amino acid sequence known as the "maturation" cleavage site. Recently, EP 514,830, published November 25, 1992, describes a virus-specific serine protease which has a role in herpesvirus replication. Additionally, Lui and Roizman (*J. Virol*, 65, 5149 (1991)) describe the sequence and activity of a protease and the associated assembly protein encoded by U_L26 of HSV-1. A. R. Welch et al. (*Proc. Natl. Acad. Sci. USA*, 88, 10792 (1991) and WO93/01291, published January 21, 1993) describe the related protease (also known as assemblin) and assembly protein encoded by U_L80 of CMV. An approach currently being investigated for potential use in the treatment of herpesvirus infections is the development of inhibitors of herpesvirus proteases.

4*H*-3,1-Benzoxazinones have been described in the literature as having serine protease activity, among others. For example, Teshima et al. (*J. Biol. Chem.*, 257, 5085-5091 (1982)) describes various 2-alkyl-4H-3,1-benzoxazin-4-ones as enzyme inhibitors. Moorman and Abeles (*J. Amer. Chem. Soc.*, 104, 6785-6786 (1982)) describes 4H-3,1-benzoxazin-2,4-dione as having some enzyme inhibitory activity. R. Stein, et al. (*Biochemistry*, 26, 4126-4130, (1987)) describes 2-alkyl-4H-benzoxazin-4-ones, with further substitution at the 5, 6 and 7 positions, as inhibiting the elastase enzyme. WO 92/18488 (published October 29, 1992) describes 2-alkyl-4H-3,1-benzoxazin-4-ones with substitution at the 5 and 7 positions as selective inhibitors of elastase. EP Pub. 206,323 (published December 30, 1985) describes 2-alkoxy-, 2-aryloxy- and 2-aralkoxy-4H-3,1-benzoxazin-4-ones, having substitution at the 5, 6, 7 and 8 positions, as enzyme inhibitors. USP 4,745,116 to A. Kranz et al. describes 2-alkoxy, 2-aryloxy- and 2-aralkoxy-4H-3,1-benzoxazin-4-ones, having further substitution at the 5, 7 and 8 positions, as enzyme inhibitors. USP 5,428,021 to Hiebert et al. describes 6-(aminoacid)amino-2-alkoxybenzoxazinones as elastase inhibitors. WO 96/07648, published March 14, 1996, describes 2-phenylamino-benzoxaziones for the treatment of Alzheimer's, and specifically 6-chloro-2-(2-iodophenylamino)-benzo[d][1,3]oxazin-4-one is described.

2-Amino-4*H*-3,1-benzoxazinones have been described. A. Krantz et al. (*J. Med. Chem.*, 33, 464-479 (1990)) describes 4H-3,1-benzoxazin-4-ones substituted with alkyl, alkylamino, alkoxy and alkylthio substituents at the 2-position, and with further substitution at the 5, 6 and 7 positions, as elastase inhibitors. Uejima et al. (*J. Pharm. Exp. Ther.*, 265, 516-522 (1993)) describe 2-alkylamino-5-methyl-7-acylamino-4H-3.1-benzoxazin-4-ones as highly selective elastase inhibitors with significant plasma stability. USP 4,657,893 to Krantz et al. describes 2-alkylamino- and 2-alkylurido-4H-3,1-benzoxazin-4-ones having further substitution at the 5,7 and 8 positions, as enzyme inhibitors.

F. L. M. Alvarez (*An. Quim.*, 79, 115-17 (1983)) describes the preparation of 2-sulfonylamino-4*H*-3,1-benzoxazinones. J. G. Tercero et al. (*An. Quim.*, 83, 247-50, (1987)) describes the preparation of 2-arylsulfonylamino-4*H*-3,1-benzoxazinones.

I. Butula et al. (*Croat. Chem. Acta*, 54, 105-8 (1981)) describe the synthesis of 2-alkylamino-4*H*-3,1-benzoxazinones. H. Urich et al. (*J. Org. Chem.*, 32, 4052-53 (1967)) describes the synthesis of 2-alkylamino-4*H*-3,1-benzoxazinones. E. Papadopoulos (*J. Heterocyclic. Chem.*, 21, 1411-14 (1984)) describes the use of 2-haloalkylamino-4*H*-3,1-benzoxazin-4-one as a starting material for the synthesis of phenylureas. EP Appln. 466,944 (published January 22, 1992) describes 2-alkylamino-7-acylamino-5-alkyl-4H-benzoxazin-4-ones as selective enzyme inhibitors of elastase.

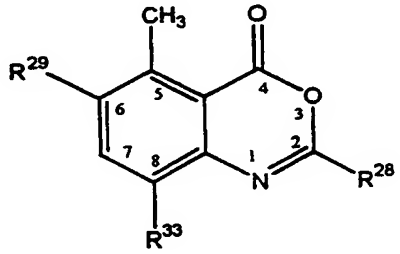
M. Badawy et al. (*J. Heterocyclic. Chem.*, 21, 1403-4 (1984)) describe the use of N-phenyl-2-amino-4*H*-3,1-benzoxazin-4-one as a starting material for the synthesis of quinazolines. R. Khan et al. (*J. Chem. Research(S)*, 342-43 (1992) describe the synthesis of 2-[5-aryl-1,3,4-oxadiazol-2-yl]amino-4*H*-3,1-benzoxazin-4-ones.

WO 96/37485 describes antiviral agents and compounds, compositions, and methods for treating herpes-related disorders. This document does not describe compounds that have specificity to HSV.

Summary of the Invention

It was discovered that specific compounds that fall within the generic scope of Formula II of WO 96/37485 are very effective against HSV at lower concentrations than the compounds of the examples specifically disclosed in WO 96/37485. The compounds of the present invention have specificity to HSV. This specificity is deemed to be derived from structural conformation of the compounds having R^{28} and R^{29} substituents.

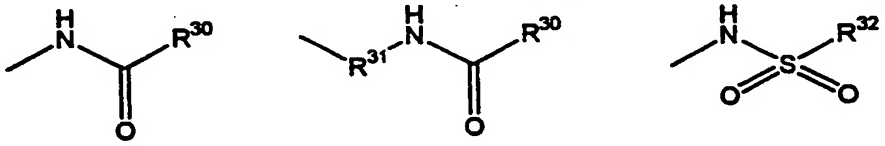
The present invention is directed to a compound of Formula II:



II

wherein R^{28} is selected from amino optionally substituted with two radicals selected from alkyl, aralkyl, heterocyclylalkyl, heterocyclyl, and aryl;

wherein R^{29} is selected from



wherein R^{30} is selected form alkyl, alkoxy, alkylamino, carboxyalkyl, alkoxyalkyl, alkylaminoalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aralkyl, aralkoxy, aryloxy, cycloalkyloxy, arylamino, aralkenyl, heterocyclylalkoxy, alkylaminoalkoxy, alkylaminoalkylamino, heterocyclylalkylamino, N-aryl-N-alkylamino, and N-aralkylamino; wherein R^{31} is alkyl; wherein R^{32} is selected from alkyl and aryl; and wherein R^{33} is selected from hydrido, halo and alkyl;

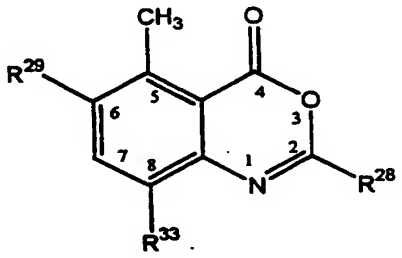
or a pharmaceutically-acceptable salt thereof.

The present invention is further directed to a pharmaceutical composition comprising a therapeutically-effective amount of a compound of formula II and a pharmaceutically acceptable carrier or diluent.

The present invention is further directed to a method or therapeutic or prophylactic treatment of Herpes Simplex Virus in a subject, said method comprising treating said subject with an effective amount of a compound of formula II.

Detailed Description of the Invention

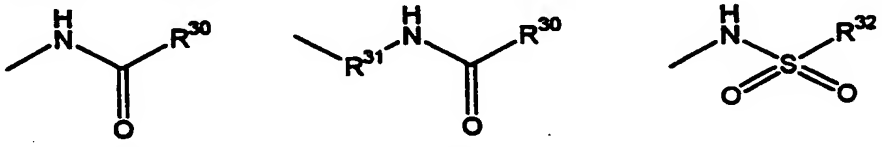
The present invention relates to a class of substituted benzoxazinones, useful in the therapeutic and prophylactic treatment of Herpes Simplex Virus viral infections, as defined by Formula II:



II

wherein R^{28} is selected from amino optionally substituted with two radicals selected from alkyl, aralkyl, heterocyclylalkyl, heterocyclyl, and aryl, or the nitrogen can form a member of a heterocyclic ring;

wherein R^{29} is selected from

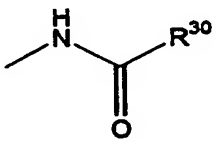
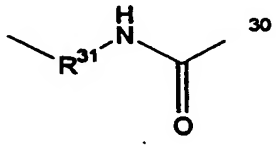
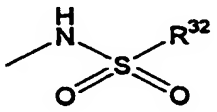


wherein R^{30} is selected form alkyl, alkoxy, alkylamino, carboxyalkyl, alkoxyalkyl, alkylaminoalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aralkyl, aralkoxy, aryloxy, cycloalkyloxy, arylamino, aralkenyl, heterocyclylalkoxy, alkylaminoalkoxy, alkylaminoalkylamino, heterocyclylalkylamino, N-aryl-N-

alkylamino, and N-aralkylamino; wherein R^{31} is alkyl; wherein R^{32} is selected from alkyl and aryl; and wherein R^{33} is selected from hydrido, halo and alkyl;

or a pharmaceutically-acceptable salt thereof.

An even more preferred class of compounds consists of those compounds of Formula II wherein R^{28} is selected from amino optionally substituted with two radicals selected from lower alkyl, lower aralkyl, lower heterocyclylalkyl, heterocyclyl, and aryl, wherein R^{29} is selected from

wherein R^{30} is selected from lower alkyl, lower alkoxy, lower alkylamino, lower carboxyalkyl, lower alkoxyalkyl, lower alkylaminoalkyl, lower cycloalkyl, heterocyclyl, lower heterocyckylalkyl, lower heterocyclylalkoxy, lower aralkenyl, lower aralkyl, lower aralkoxy, phenyloxy, phenylamino, lower cycloalkyloxy, lower N-phenyl-N-alkylamino, lower alkylaminoalkoxy, lower alkylaminoalkylamino, lower heterocyclylalkylamino, and lower N-aralkylamino; wherein R^{31} is lower alkyl; wherein R^{32} is selected from lower alkyl and aryl; and

wherein R^{33} is selected from hydrido and lower alkyl; or a pharmaceutically-acceptable salt thereof.

Most preferred are compounds where R^{28} is selected from the group consisting of methyl(phenylmethyl)amino, methyl[(4-methoxyphenyl)-methyl]amino, 1-(1,2,3,6-tetrahydro-pyridyl), isopropyl(methyl)amino, (4-furoyl)piperazinyl, (2-cyano)ethyl, (4-thenoyl)piperazinyl, (4-benzenesulfonyl)-piperazinyl, diisopropylamino, [methyl(4-dimethylamino)phenylmethyl]amino, methyl(2-pyridylmethyl)-amino; methyl[2-(3-indolyl)ethyl]amino, 4-morpholyl, allyl(methyl)amino, 1-decahydroquinolyl, and 4-(1-acetylpiperadinyl); and R^{29} is selected from the group consisting of [(1,1-dimethylethoxy)carbonyl]amino, benzoylamino, (phenylmethoxyacetyl)amino, and (2,4,6-Trifluorobenzoyl)amino.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene ($-CH_2-$) radical. Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl", "hydroxyalkyl" and "aralkyl" the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most Preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, iso-amyl, hexyl and the like.

The term "halo" means halogens such as fluorine, chlorine, bromine, or iodine.

The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy.

The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxyalkyl radicals are "lower alkoxyalkyl" radicals having one to six carbon atoms and one or two alkoxy radicals. Examples of such radicals include methoxymethyl, methoxyethyl, ethoxyethyl, methoxybutyl and methoxypropyl. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" or haloalkoxyalkyl radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", alon or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused.

The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, aralkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, heterocyclylalkoxy, alkylaminoalkoxy, carboxyamino, carboxyaminoalkyl, carboxyaminoaralkyl, amino, halo, nitro, alkylamino, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkylsulfonylamino, arylsulfonylamino, acyl, cyano, carboxy, aminocarbonyl, alkylaminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl.

The terms "heterocyclyl" or "heterocyclic" embrace saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include saturated 5 to 7-membered heteromonocyclic group containing 1 to 4 nitrogen atoms (e.g., pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, tropanyl, homotropanyl, etc.); saturated 5 to 7-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., morpholinyl, etc.); saturated 5 to 7-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl, etc.). Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, oxazolinyl, dihydrofuran and dihydrothiazole. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include unsaturated 5 to 7-membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, azepinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl,

indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo [1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-m mbered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 5 to 7-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc; unsaturated 5 to 7 membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 5 to 7-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuryl, benzothienyl, and the like. Said "heterocyclyl" radicals may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, aralkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, alkylaminoalkoxy, aminocarboxy, alkylaminocarboxy, aralkylaminocarboxy, amino, halo, nitro, alkylamino, alkylcarbonylamino, arylcarbonylamino, alkoxycarbonylamino, aralkoxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkylsulfonylamino, arylsulfonylamino, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl. More preferred heteroaryl radicals include 5 to 6-membered heteroaryl radicals.

The term "cycloalkyl" embraces radicals having 3 to 10 carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having 3 to 7 carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl"

embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkylsulfonyl" radicals. More preferred haloalkylsulfonyl radicals are "lower haloalkylsulfonyl" radicals having one or more halo atoms attached to lower alkylsulfonyl radicals as described above. Examples of such lower haloalkylsulfonyl radicals include fluoromethylsulfonyl, trifluoromethylsulfonyl, and chloromethylsulfonyl. The term "arylsulfonyl" embraces aryl radicals as defined above, attached to a sulfonyl radical. Examples of such radicals include phenylsulfonyl. The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denotes NH_2O_2S.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", donotes $-CO_2H$.

The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes - (C=O)-. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Preferably, "lower alkoxycarbonyl" embraces alkoxy radicals having one to six carbon atoms. Examples of such "lower alkoxycarbonyl" ester radicals include substituted and unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, and hexyloxycarbonyl.

The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having 1 to 6 carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. The aryl in the aralkyl may be additionally substituted as described above.

The term "aralkenyl" embraces aryl-substituted alkenyl radicals. Preferable aralkenyl radicals are "lower phenylalkenyl" radicals having phenyl radicals attached to alkenyl radicals having 1 to 6 carbon atoms. Examples of such radicals include phenylethenyl and phenylpropenyl. The aryl in said aralkyl may be additionally

substituted as described above. The terms benzyl and phenylmethyl are interchangeable.

The term "alkylcarbonyl" includes radicals having alkyl radicals as defined above, attached to a carbonyl radical. More preferred alkylcarbonyl radicals are "lower alkylcarbonyl" radicals having one to six carbon atoms. Examples of such radicals include methylcarbonyl and ethylcarbonyl.

The term "carboxyalkyl" embraces radicals having a carboxy radical as defined above, attached to an alkyl radical. The alkanoyl radicals may be substituted ro unsubstituted, such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, trifluoroacetyl or the like, in which the preferable one is formyl, acetyl, propionyl or tribfluoroacetyl.

The term "heterocyclylalkyl" embraces heterocyclic-substituted alkyl radicals. More preferred heterocyclylalkyl radicals are "lower heterocyclylalkyl" radicals having 5 to 6 membered heterocyclyl radicals attached to lower alkyl radicals having 1 to 6 carbon atoms. Examples of such radicals include pyrrolidinylmethyl, piperidinylmethyl, morpholinylmethyl, piperazinylmethyl, oxazolylmethyl, oxazolylethyl, oxazolinylmethyl, oxazolinylethyl, indolylethyl, indolylmethyl, pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl and quinolylethyl. The heterocyclic in said heterocyclylalkyl may be additionally substituted as described above.

The term "aryloxy" embraces aryl radicals, as defined above, attached to an oxygen atom. The aryl in said aryloxy may be additionally substituted as described above. Examples of such radicals include phenoxy.

The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. The "aralkoxy" radical may be further substituted on the aryl ring portion of the radical.

The term "alkylamino" denotes amino groups which have been substituted with 1 or 2 alkyl radicals. More preferred alkylamino radicals are "lower alkylamino" having alkyl radicals of 1 to 6 carbon atoms attached to the nitrogen atom of an amine. Suitable "lower alkylamino" may be mono or dialkylamino such

as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like.

The term "alkylaminoalkyl" denotes alkylamino groups, as defined above, attached to an alkyl radical. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" having 1 to 6 carbon atoms attached to a lower aminoalkyl radical as described above. Suitable "lower alkylaminoalkyl" may be mono or dialkylaminoalkyl radicals such as N-methylaminomethyl, N-ethylaminomethyl, N,N-dimethylaminomethyl, N,N-dimethylaminoethyl N,N-dimethylaminopropyl or the like.

The term "dialkylaminoalkyl" also includes radicals where the bridging alkyl moiety is optionally substituted with alkylsulfonyl, alkoxy, aralkoxy, heterocyclyl, and aryl.

The term "alkylaminoalkoxy" denotes alkylamino groups, as defined above, attached to an alkoxy radical. Suitable "alkylaminoalkoxy" may be mono or dialkylaminoalkoxy radicals such as N-methylaminomethoxy, N-ethylaminomethoxy, N,N-dimethylaminomethoxy, N,N-dimethylaminoethoxy N,N-dimethylaminopropoxy or the like.

The term "alkylaminocarbonyl" embraces alkylamino radicals, as described above, to a carbonyl radical. More preferred alkylaminocarbonyl radicals are "lower alkylaminocarbonyl" having lower alkylamino radicals, as described above, attached to a carbonyl radical. Examples of such radicals include N-methylaminocarbonyl and N,N-dimethylaminocarbonyl.

The term "arylamino" denotes amino groups which have been substituted with 1 or 2 aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical.

The terms "N-arylaminoalkyl" and "N-aryl-N-alkyl-aminoalkyl" denote amino groups which have been substituted with one aryl radical or one aryl and one alkyl radical, respectively, and having the amino group attached to an alkyl radical. More preferred arylaminoalkyl radicals are "lower arylaminoalkyl" having the arylamino radical attached to 1 to 6 carbon atoms. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl.

The term "aminocarbonyl" denotes an amide group of the formula -C(=O)NH_2. The term "aminocarbonylalkyl" denotes an aminocarbonyl group attached to an alkyl radical. More preferred are "lower aminocarbonylalkyl" having lower aminocarbonyl radicals as described above attached to alkyl of one to six carbon atoms. The term "alkylaminocarbonylalkyl" denotes an aminocarbonyl group which has been substituted with one or two alkyl radicals and attached to an alkyl radical. More preferred are "lower alkylaminocarbonyalkyl" having lower alkylaminocarbonyl radicals as described above attached to alkyl radicals of one to six carbon atoms.

The term "aryloxy" embraces aryl radicals attached to a divalent oxygen atom, that is, to form monoaryloxy and diaryloxy radicals. The more preferred aryloxy radicals are "lower aryloxy". An example includes phenoxy.

"Amino acid residue" means any of the naturally occurring alpha-, beta- and gamma-amino carboxylic acids, including their D and L optical isomers and racemic mixtures thereof, synthetic amino acids, and derivatives of these natural and synthetic amino acids. The amino acid residue is bonded through a nitrogen of the amino acid. The naturally occurring amino acids which can be incorporated in the present invention include, but are not limited to, alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, proline, serine, threonine, thyroxin, tryptophan, tyrosine, valine, β-alanine, and γ-aminobutyric acid. Derivatives of amino acids which can be incorporated in the present invention include, but are not limited to, amino acids having protected and modified carboxylic acids, including acid esters and amides, protected amines, and substituted phenyl rings, including but not limited to alkyl, alkoxy and halo substituted tyrosine and phenylalanine.

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formula II in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of therapeutic and prophylactic treatment of viral infections, particularly herpetoviridae infection, in a

subject, the method comprising treating the subject having such herpes infection a therapeutically-effective amount of a compound of Formula II.

The present invention also comprises a method of inhibiting a viral protease, the method comprising administering a therapeutically-effective amount of a compound of Formula II.

Also included in the family of compounds of Formula II are the stereoisomers and tautomers thereof. Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. Accordingly, some of the compounds of this invention may be present in racemic mixtures which are also included in this invention. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts.

A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting an amine functionality of precursors to compounds of Formula II with an optically pure acid in an activated form or an optically pure acid in an activated form or an optically pure isocyanate. Alternatively, diastereomeric derivatives can be prepared by reacting a carboxyl functionality of precursors to compounds of Formula II with an optically pure amine base. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of Formula II can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt. Additional methods for resolving optical isomers, known t those

skilled in the art may be used, for example, those discussed by Jaques et al. in *Enantiomers, Racemates, and Resolutions*, John Wiley and Sons, New York (1981).

Also included in the family of compounds of Formula II are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula II may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, *p*-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethylsulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula II include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, choline, chloroprocaine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula II by reacting, for example, the appropriate acid or base with the compound of Formula II.

Also embraced within this invention is a class of pharmaceutical compositions comprising one or more compounds of Formula II in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active

ingredients. The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and composition may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

The amount of therapeutically active compound that is administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The pharmaceutical compositions may contain active ingredient in the range of about 0.1 to 2000 mg, preferably in the range of about 0.5 to 500 mg and most preferably between about 1 and 100 mg. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably between about 1 to 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-

release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut, oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

For infections of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in a total amount of, for example, 0.075 to 30 % w/w, preferably 0.2 to 20 % w/w and most preferably 0.4 to 15 % w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least 30 % w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the

recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations in very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-thylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The antiviral active ingredients are preferably present in such formulations in a concentration of 0.5 to 20 %, advantageously 0.5 to 10 % and particularly about 1.5 % w/w.

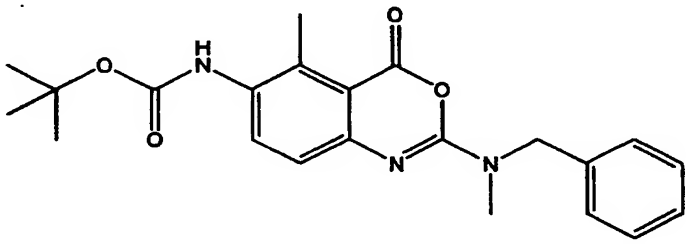
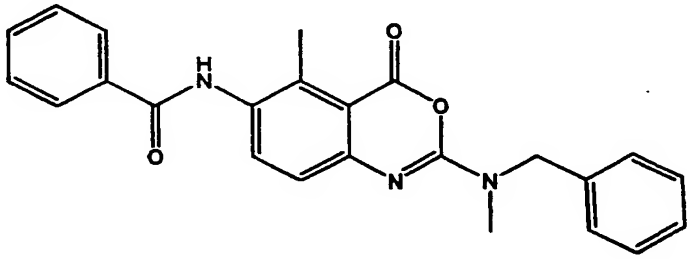
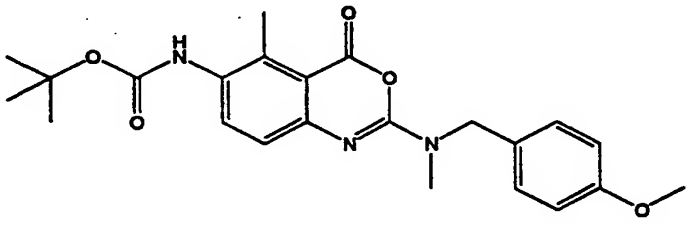
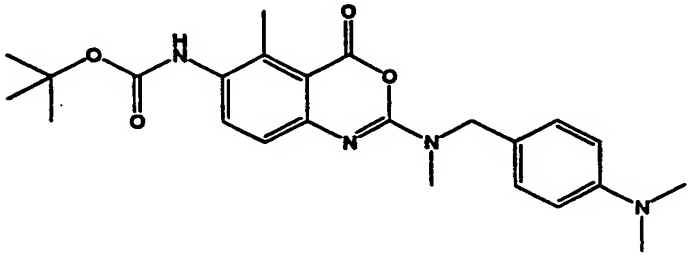
Examples

The following examples contain detailed descriptions of the methods of preparation of compounds of Formula II. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated.

The following abbreviations are used:

EtOAc	ethyl acetate
HCl	hydrochloric acid
DMSO	dimethylsulfoxide
d_6-DMSO	deuterated dimethylsulfoxide
$CDCl_3$	deuterated chloroform
$CHCl_3$	chloroform
CD_3OD	deuterated methanol
Et_2O	diethyl ether
$MgSO_4$	magnesium sulfate
H_2SO_4	sulfuric acid
$NaHCO_3$	sodium bicarbonate
$KHSO_4$	potassium hydrogen sulfate
NMM	N-methylmorpholine
DMF	dimethylformamide
DMAP	4-dimethylaminopyridine
CDI	carbonyldiimidazole
NaOH	sodium hydroxide
KOH	potassium hydroxide
LiOH	lithium hydroxide
$Pd(OH)_2/C$	palladium hydroxide on carbon
Pd/C	palladium on carbon
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide·HCl
BOC	*tert*-butyloxycarbonyl
TLC	thin layer chromatography
MeOH	methanol
KI	potassium iodide
CH_2Cl_2	methylene chloride

The following is a list of inv ntive compounds and comparative compounds.

Comp und	Formula
1	
2	
3	
4	

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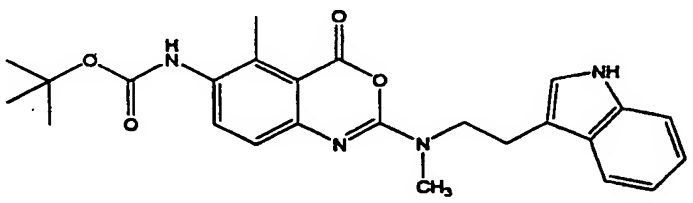
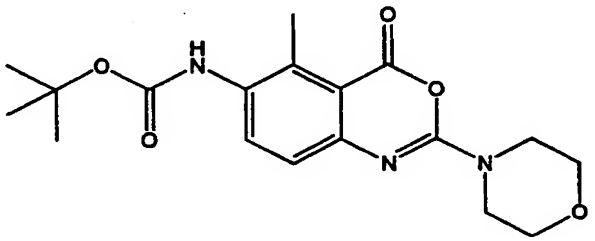
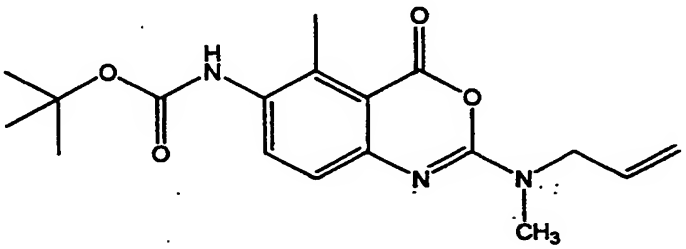
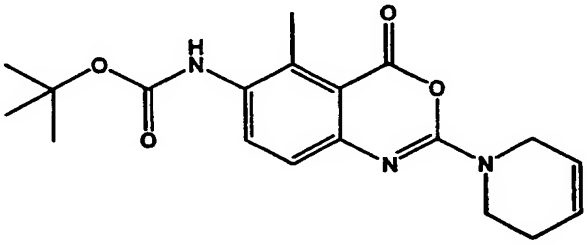
5	
6	
7	
8	

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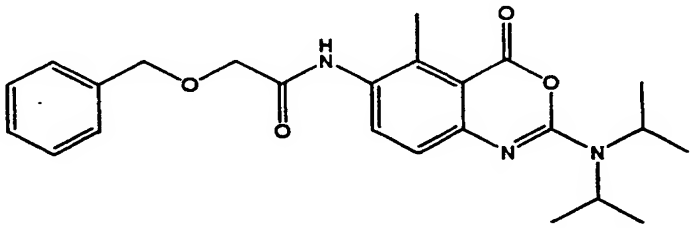
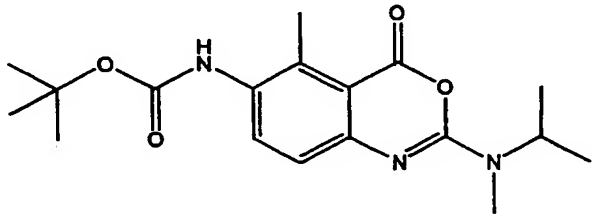
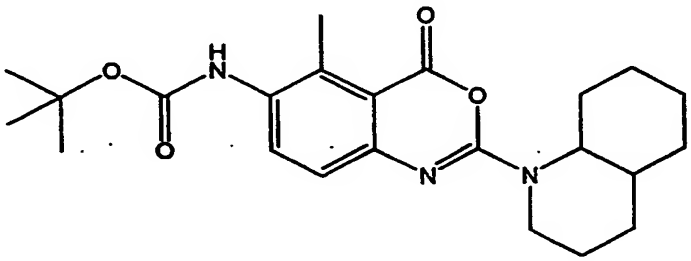
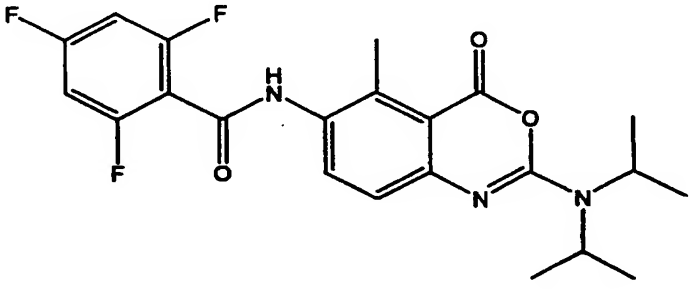
9	
10	
11	
12	

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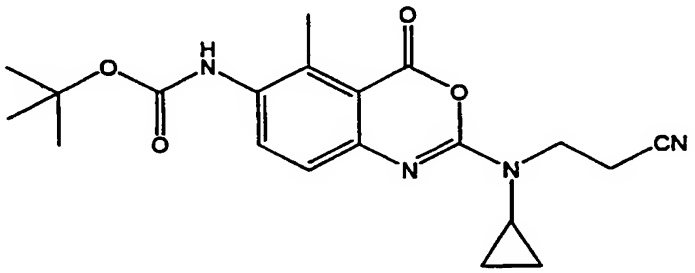
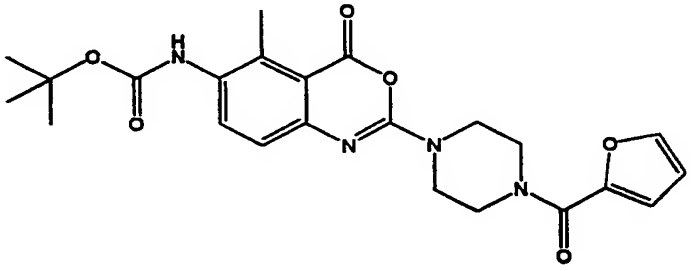
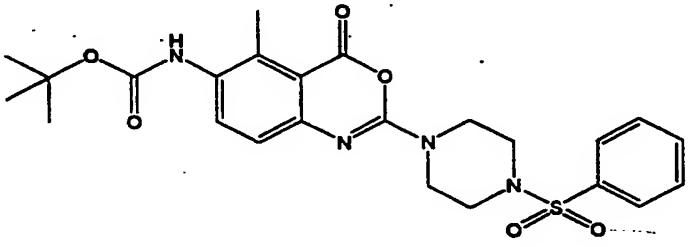
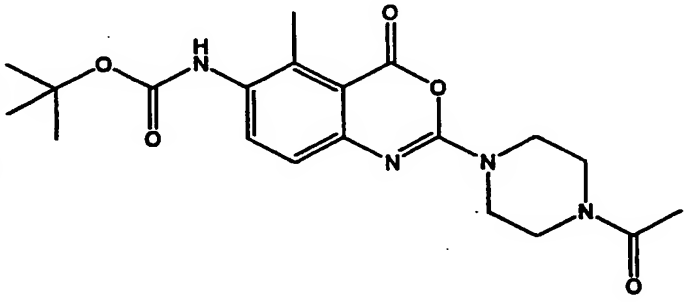
13	
14	
15	
16	

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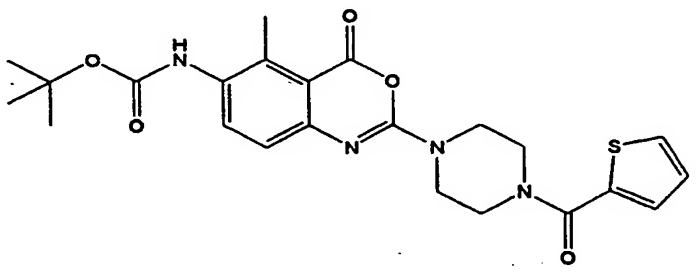
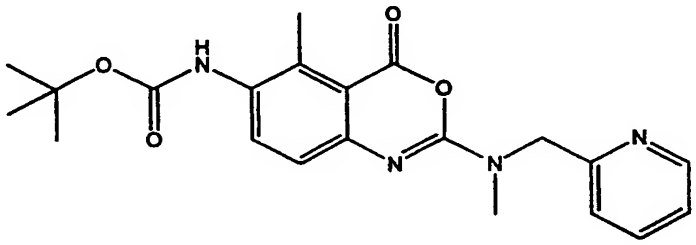
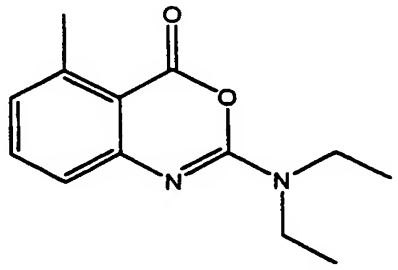
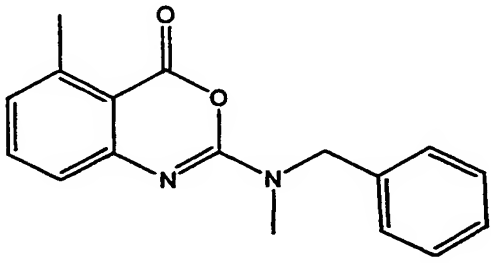
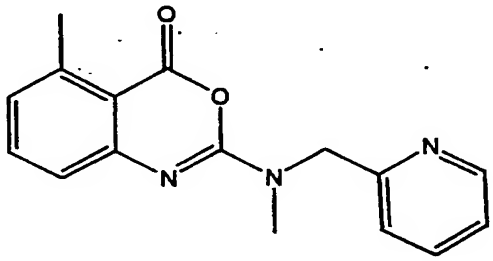
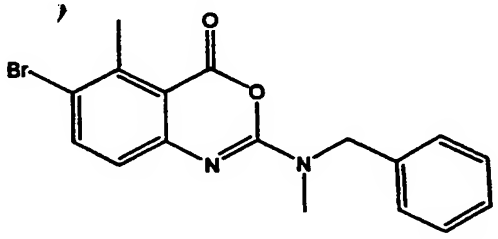
17	
18	

Comparative Compound	Formula
CC 1	
CC 2	
CC 3	
CC 4	

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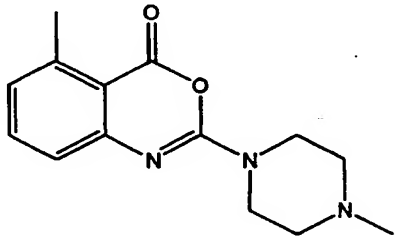
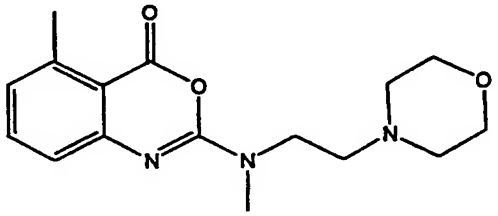
CC 5	
CC 6	

Example 1

Compound 1

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[methyl(phenylmethyl)amino]-4H-3,1-benzoxazin-4-one

A. Preparation of 3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-methyl-6-[[[methyl(phenylmethyl)-amino]carbonyl]amino]benzoic acid, 2-(trimethylsilyl)ethyl ester.

To a solution of 6-amino-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-methylbenzoic acid, 2-(trimethylsilyl)ethyl ester (0.11 mmol in 3ml of CH_2Cl_2), was added a solution of p-Nitrophenyl chloroformate (0.1 mmol, 20.2 mg) in CH_2Cl_2 (0.2 ml). After stirring at room temperature for 3 hours, resulting solution was washed with 1N-HCl, water, and dried over $MgSO_4$. To this solution of activated carbamate, methyl(phenylmethyl)amine (0.016 ml, 0.12 mmol) was added. After stirring at room temperature for 15 hours, a solution of tetrafluorophthalic anhydride (15 mg, 0.07 mmol) in CH_2Cl_2 (0.7 ml) was added and stirred for 3 hours, followed by polyamine resin prepared by the method of L. Flynn et al. (*J. Amer. Chem. Soc.*, 119, 4874-4881 (1997)) (200 mg, 0.6 mmol). After 1 hour, the

mixture was filtrated and concentrated, dissolved in CH_2Cl_2 again, Amberlyst A-21 (50 mg) was added, stirred for 1 hour. Resin was removed with filtration, the solution was concentrated to afford white crystal (38.7 mg). ^{1}H-NMR (270MHz, $CDCl_3$) δ 0.06(s, 9H), 1.0-1.1(m, 2H), 1.50(s, 9H), 2.28(s, 3H), 2.99(s, 3H), 4.3-4.4(m, 2H), 4.59(s, 2H), 6.15(br.s, 1H), 7.2-7.3(m, 5H), 7.67(br.d, 1H, J=9Hz), 8.01(d, 1H, J=9Hz), 8.25(s, 1H), HPLC(A) retention time=26.8min.

B. Preparation of 3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-methyl-6-[[[methyl(phenylmethyl)-amino]carbonyl]amino]benzoic acid.

To a solution of the product of step A(38.7 mg) in 3 ml of THF was added a solution of TBAF in THF (1.0 M, 0.12 ml, 0.12 mmol) and stirred at room temperature for 1 hour. Amberlyst A-15 H form (200 mg), Amberlyst A-15 calcium form (200 mg) were added, shaken overnight, filtrated, and concentrated to afford white crystal (26.0 mg). ^{1}H-NMR (270MHz, CD_3OD) δ 1.42(s, 9H), 2.24(s, 3H), 2.89(s, 3H), 4.50(s, 2H), 7.1-7.3(m, 6H), 7.64(d, 1H, J=9Hz), HPLC(A) retention time=15.4 min.

C. 6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[methyl(phenylmethyl)-amino]-4H-3,1-benzoxazin-4-one

To a solution of the product of step B(26.0 mg) in 4 ml of DMF was added P-EDC (300 mg, 0.3 mmol), stirred for 2 hours. Filtrated, concentrated to afford white crystal (21. 5mg). ^{1}H-NMR (270MHz, $CDCl_3$) δ 1.51(s, 9H), 2.65(s, 3H), 3.08(s, 3H), 4.74(s, 2H), 6.26(br.s, 1H), 7.12(d, 1H, J=9Hz), 7.2-7.4(m, 5H), 7.83(br.d, 1H), HPLC(A) retention time=24.7min, MS(MH+)=396.

A similar method was used to prepare the following compounds

Compound 3

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[methyl[(4-methoxyphenyl)methyl]amino]-4H-3,1-benzoxazin-4-one. ^{1}H-NMR (270MHz, $CDCl_3$) δ 1.51(s, 9H), 2.65(s, 3H), 3.06(s, 3H), 3.80(s, 3H), 4.67(s, 2H), 6.23(br.s,

1H), 6.87(d, 2H, J=9Hz), 7.12(d, 1H, J=9Hz), 7.25(d, 2H, J=9Hz), 7.83(br.d, 1H), HPLC(B) retention time=8.26 min, MS(MH+)=426.

Compound 8

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[1-(1,2,3,6-tetrahydro-pyridyl)]-4H-3,1-benzoxazin-4-one.

HPLC(A) retention time=18.4 min, MS(MH+)=358.

Compound 10

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[isopropyl(methyl)amino]-4H-3,1-benzoxazin-4-one.

HPLC(A) retention time=22.9 min.

Compound 14

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[(4-furoyl)piperazinyl]-4H-3,1-benzoxazin-4-one.

HPLC(A) retention time=20.0 min.

Compound 13

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[(2-cyanoethyl)-(cyclopropyl)amino]-4H-3,1-benzoxazin-4-one.

HPLC(A) retention time=21.0 min.

Compound 17

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[(4-thenoyl)piperazinyl]-4H-3,1-benzoxazin-4-one.

HPLC(B) retention time=7.02 min.

Compound 15

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[(4-benzenesulfonyl)-piperazinyl]-4H-3,1-benzoxazin-4-one.

HPLC(B) retention time=7.88 min.

Example 2

Compound 2

6-(benzoylamino)-5-methyl-2-[methyl(phenylmethyl)amino]-4H-3,1-benzoxazin-4-one

A. Preparation of 3-amino-2-methyl-6-[[[methyl(phenylmethyl)amino]-carbonyl]amino]-benzoic acid, 2-(trimethylsilyl)ethyl ester.

To a solution of the product of example 1-step A (40.2 mg) in 1,4-doixane (2 ml) was added 4N-HCl solution in 1,4-dioxane (2 ml). After stirred at room temperature for 2 hours, the reaction mixture was concentrated. CH_2Cl_2 (4 ml) and DMF (0.5 ml) was added, dissolved, and Amberlyst A-21 (100 mg) was added. Shaken for 1 hour, the resin was filtered off, concentrated to afford 35.7 mg of product. ^{1}H-NMR (270MHz, $CDCl_3$) δ 0.06(s, 9H), 0.9-1.0(m, 2H), 2.18(s, 3H), 3.97(s, 3H), 4.2-4.3(m, 2H), 4.58(s, 2H), 6.79(d, 1H, J=8.9Hz), 7.2-7.4(m, 5H), 7.77(d, 1H, J=8.9Hz), 8.14(s, 1H), HPLC(A) retention time=23.4min.

B. Preparation of 3-(benzoylamino)-2-methyl-6-[[[methyl(phenylmethyl)amino]-carbonyl]amino]-benzoic acid, 2-(trimethylsilyl)ethyl ester.

To a solution of the product of step A (35.7 mg) in 2 ml of CH_2Cl_2, were added pyridine (0.011 ml, 0.14 mmol), benzoyl chloride (0.014 ml, 0.12 mmol). After stirring at room temperature for 14 hours, polyamine resin (200 mg, 0.6 mmol) was added, stirred for 2 hours. Filtration and concentration afforded 32.3 mg of the product. ^{1}H-NMR (270MHz, $CDCl_3$) δ 0.06(s, 9H), 1.0-1.1(m, 2H), 2.33(s, 3H), 2.98(s, 3H), 4.2-4.3(m, 2H), 4.57(s, 2H), 7.2-7.6(m, 9H), 7.8-7.9(m, 3H), 8.07(d, 1H, J=9Hz), 8.84(s, 1H), HPLC(A) retention time=25.4min.

C. Preparation of 3-(benzoylamino)-2-methyl-6-[[[methyl(phenylmethyl)-amino]-carbonyl]amino]-benzoic acid.

To a solution of the product of step B (32.3 mg) in 3ml of THF was added a solution of TBAF in THF (1.0 M, 0.12 ml, 0.12 mmol) and stirred at room temperature for 1 hour. Amberlyst A-15 H form (200 mg), Amberlyst A-15 calcium form (200 mg) were added, shaken overnight, filtrated, and concentrated to afford white crystal (25.4 mg). ^{1}H-NMR (270MHz, $CDCl_3$) δ 2.19(s, 3H), 2.90(s, 3H), 4.52(s, 2H), 7.2-7.5(m, 7H), 7.77(d, 1H, J=9Hz), 7.9(m, 2H), 8.58(s, 1H), 8.96(br.s, 1H).

D. 6-(benzoylamino)-5-methyl-2-[methyl(phenylmethyl)amino]-4H-3,1-benzoxazin-4-one.

To a solution of the product of step C (25 mg) in 4ml of DMF was added P-EDC (300 mg, 0.3 mmol), stirred for 2 hours. Filtrated, concentrated to afford white crystal (15.8 mg). ^{1}H-NMR (270MHz, $CDCl_3$) δ 2.69(s, 3h), 3.01(s, 3H), 4.75(s, 2H), 7.16(d, 1H, J=9Hz), 7.2-7.6(m, 8H), 7.8-8.0(m, 4H), HPLC(A) retention time=22.4 min., MS(MH+)=400.

Compound 9

6-[(Phenylmethoxyacetyl)amino]-5-methyl-2-(diisopropylamino)-4H-3,1-benzoxazin-4-one.

HPLC(A) retention time=24.1 min.

Compound 12

6-[(2,4,6-Trifluorobenzoyl)amino]-5-methyl-2(diisopropylamino)-4H-3,1-benzoxazin-4-one.

HPLC(A) retention time=23.3 min.

Example 3

Compound 4

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[[[4-(dimethylamino)phenyl]methyl]methylamino]-4H-3,1-benzoxazin-4-one.

A. Preparation of 3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-methyl-6-[[[N-[[4-(dimethylamino)phenyl]methyl]methylamino]carbonyl]amino]benzoic acid, 2-(trimethylsilyl)ethyl ester.

Proceeding in a manner similar to example 1A, substituting methyl(phenylmethyl)amine with N-[(4-dimethylamino)phenyl]methyl]methylamine. ^{1}H-NMR(270 MHz, $CDCl_3$) d 0.06(s, 9H), 1.0-1.1(m, 2H), 1.50(s, 9H), 2.28(s, 3H), 2.93(s, 9H), 4.2-4.3(m, 2H), 4.48(s, 2H), 6.11(br.s, 1H), 6.70(d, 2H, J=9Hz), 7.19(d, 2H, J=9Hz), 7.58(br.d, 1H), 8.06(d, 1H, J=9Hz), 8.62(br. S, 1H).

B. Preparation of 6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[[[4-(dimethylamino)phenyl]methyl]methylamino]-4H-3,1-benzoxazin-4-one.

To a solution of the product of step A (521 mg, 0.935 mmol) in 10 ml of THF, was added a solution of tetrabutylammonium fluoride in THF (1.0 M, 1.12 ml, 1.12 mmol). Stirred at room temperature for 45 min., acetyl chloride (0.12 ml, 1.7 mmol) was added, and stirred for 1.5 hours. Concentrated, purified over silica gel, washed with saturated $NaHCO_3$ aqueous solution to afford white amorphous solid (241 mg). ^{1}H-NMR (270MHz, $CDCl_3$) d 1.51(s, 9H), 2.65(s, 3H), 2.93(s, 6H), 3.11(s, 3H), 4.63(s, 2H), 6.21(br.s, 1H), 6.69(d, 2H, J=9Hz), 7.12(d, 1H, J=9Hz), 7.19 (d, 2H, J=9Hz), 7.82(br.d, 1H, J=9Hz), HPLC(B) retention time=8.62 min, MS(MH+)=439.

Compound 18

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[methyl(2-pyridylmethyl)-amino]-4H-3,1-benzoxazin-4-one.

HPLC(B) retention time=6.71 min., MS(MH+)=397.

Compound 5

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[methyl[2-(3-indolyl)ethyl]amino]-4H-3,1-benzoxazin-4-one.

^{1}H-NMR (270MHz, $CDCl_3$) δ 1.52(s, 9H), 2.65(s, 3H), 3.1(m, 5H), 3.82(t, 2H, J=7Hz), 6.21(br.s, 1H), 7.0-7.4(m, 4H), 7.7-8.1(m, 3H). HPLC(B) retention time=8.08min., MS(MH^+)=449.

Compound 6

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-(4-morpholyl)-4H-3,1-benzoxazin-4-one.

^{1}H-NMR (270MHz, $CDCl_3$) δ 1.52(s, 9H), 2.65(s, 3H), 3.72(d, 4H, J=3Hz), 3.75(d, 4H, J=3Hz), 6.25(br.s, 1H), 7.19(d, 1H, J=9Hz), 7.86(br.d, 1H, J=9Hz). HPLC(B) retention time=5.84min., MS(MH^+)=362.

Compound 7

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[allyl(methyl)amino]-4H-3,1-benzoxazin-4-one.

^{1}H-NMR (270MHz, $CDCl_3$) δ 1.41(s, 9H), 2.44(s, 3H), 2.99(s, 3H). 4.06(d, 2H, J=5Hz), 5.1-5.3(m, 2H), 5.7-6.0(m, 1H), 6.98(d, 1H, J=9Hz), 7.44(d, 1H, J=9Hz), 8.68(br.s, 1H). HPLC(A) retention time=21.88min., MS(MH^+)=346.

Compound 11

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-(1-decahydroquinolyl)-4H-3,1-benzoxazin-4-one.

HPLC(B) retention time=8.63min., MS(MH^+)=414.

Compound 16

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[4-(1-acetylpiperadinyl)]-4H-3,1-benzoxazin-4-one.

HPLC(B) retention time=4.98min., MS(MH^+)=403.

Biological Evaluation

The compounds of this invention exhibited antiviral activity as indicated by inhibition *in vitro* of herpesvirus protease and HCMV infectivity. The antiviral activity of the compounds of this invention illustrated in the Examples was determined by the following methods.

Enzymatic assay for HSV-1 protease (assemblin) inhibition

FP Assay

Assemblin protease activity was determined using fluorescence polarization (FP). The fluorescent substrate was biotin-gamma-aminobutyrate-HTYLQASERFRIK-DTAF, based on the HSV-1 release cleavage site. Incubation of this substrate with assemblin resulted in cleavage between alanine and serine. A change in molecular size of fluorescent substrate molecule, which was increased using avidin as a reaction stop reagent, allowed cleavage to be measured by FP. Potential protease inhibitors were dissolved in DMF and then diluted 5-fold in assay buffer. 6.5uL were added to the wells of a 96-well plate (U-bottom 96-well black plate, Dynatech or Costar) which was previously blocked using blocking solution (10mM Tris-HCl pH 8.0, 150mM NaCl, 0.05% Tween 20, 1mg/mL BSA). The enzyme was diluted to 21.3 ug/mL in assay buffer (1M NaCitrate, 50mM NaPhosphate, pH 7.4, 100mM NaCl, 20% glycerol, 2mM TECP) and 48.5uL were added to each well. Following a 30 minute incubation at room temperature, 10uL of 62.5ug/mL substrate were added. After about 90 minute incubation at room temperature, 50uL of 2mg/mL avidin in phosphate buffer (50mM Naphosphate, 100mM NaCl, pH 7.4) were added to each well. The plates were read by a fluorescence polarization plate reader. Inhibitor potency was determined by comparison with incubations lacking inhibitor.

HPLC assay

Assays were performed with the peptide substrate H-His-Thr-Tyr-Leu-Gln-Ala-Ser-Glu-Lys-Phe-Lys-Met-Trp-Gly-NH_2 (Bachem). This substrate is a HSV-1-amide UL26 Open Reading Frame (242-255) and is derived from the release site of HSV-1 protease. HSV-1 protease cleaves between alanine and serine. The product

SEKFKMWG was quantified on HPLC using fluorescence detection of tryptophan residue. Enzyme was diluted to 4.3ug/mL in assay buffer (1M NaCitrate, 50mM NaPhosphate, pH 7.3, 100mM NaCl, 20% glycerol, 2mM TCEP) and 48.5uL were added to the tubes. Potential protease inhibitors were dissolved in DMF and then diluted 10-fold in assay buffer. 6.5uL of inhibitor solution were added to each tube. Following a 30-minute incubation at room temperature, 10uL of substrate in phosphate buffer (50mM Naphosphate, 100mM NaCl, pH 7.4) were added to all tubes. The final concentration of the substrate in the reaction mixtures was 10uM. After a 15-minute incubation at room temperature, assays were quenched using 50uL of 50% TCA. Inhibitor potency was determined by comparison with incubations lacking inhibitor, which under these conditions gave about 20% cleavage of substrate.

Assay Components

Recombinant HSV-1 protease

HSV-1 protease was purified from baculovirus expressing a DNA construction encoding residues 1-288 of HSV-1 UL26 open reading frame and 32 heterologous amino acid. The construction also encoded six additional histidine residues at the amino terminus of the protease. These additional histidine residues provided an affinity ligand by which the protein was purified using Ni-NTA agarose gel (Qiagen). The purified protease was stored in stock solution (20mM HEPES buffer, pH 8.5, containing 20% (v/v) glycerol). This stock was diluted with assay buffer to adequate concentration of enzymatic assay.

Substrate

FP Assay

A specific substrate was synthesized based on the cleavage specificity of HSV-1 protease at the "release site" of the assembly protein (DiIanni, C.L., et al., *J. Biol. Chem.* 268, 2048, (1993)). The assembly protein release site has the sequence, HTYLQA*SEKFKMWG. The substrate used was biotin-gamma-aminobutyrate-HTYLQA*SERFRIK-DTAF which was prepared by standard peptide synthetic methods such as that described in Bodansky and Bodansky, "The

Practice of Peptide Synthesis" (1984), and was stored as a stock solution at 2.5mg/mL in DMF. This was diluted to 62.5ug/mL with phosphate buffer (50mM Naphosphate, 100mM NaCl, pH 7.4) just before use.

HPLC assay

The substrate was HSV-1-amide UL 26 Open Reading Frame (242-255), obtained from Bachem (Product No. M-2160).

Assay Buffer

An assay buffer (1M NaCitrate, 50mM NaPhosphate, pH 7.4, 100mM NaCl, 20% glycerol, 2mM TCEP) was used to dilute stock solutions of enzyme and inhibitors.

Antiviral and Cytotoxic Assay

These complimentary assays tested the ability of a compound to inhibit the production of new virus and the toxicity of the compound to the host cells. It was important that both assays be performed simultaneously in order to compare the results directly since toxicity may indirectly reduce viral replication.

Abbreviations:

DMEM - Dulbecco's Modified Eagle Medium; commercially available.

FBS - fetal bovine serum; commercially available and unknown factors necessary for growth of cells in culture.

HSV - herpes simplex virus.

Antiviral assay

The antiviral assay was estimated by plaque reduction assay performed by following methods. 1×10^5 of vero cells (African green monkey kidney cell) in 48-well plates were over-night cultured and the medium of this culture was replaced with 200 µl of 2% FBS DMEM containing 2× the desired final concentration of test compounds or no compound as control. The cultures were added 50 µl of 2% FBS DMEM containing with about 50 plaque forming units of HSV-1 and next 250 µl of 2% FBS DMEM containing 1% methylcellulose. These infected cultures were incubated at 37°C, 5% CO_2 for 3 days until plaques was visible. The cells

were fixed and stained simultaneously with 0.025% crystalviolet in 5% formalin solution and plaque were counted. The concentration of test compound which conferred 50% inhibition of plaque formation compared to no compound control was interpolated from the observed data and defined as IC_{50}. Results are included in Table 2.

Cytotoxic assay

4×10^4 of vero cells in 96-wells were over-night cultured in 100 µl of 10% FBS DMEM. These cultured cells were added 100 µl of 10% FBS DMEM containing 50 µM of test compounds or no compound as control. Cells were cultured incubated at 37°C, 5% CO_2 for 3 days. For measuring proliferation of the cells, cells were added 20 µl of alamarBlue™ and incubated for 8 hours until the color of control was changed. And then the cells were road spectrophotometically (absorbance at 570nm and 600nm) with BIO-RAD model 3550 microplate reader. The result was indicted as the ratio at 50 µM compound concentration and no compound.

Chymotripsin Assay

The chymotripsin assay was modified from the method of Delmar, et al. (Anal. Biochem. 99, 316-320 (1979)). Bovine pancreas α-chymotripsin(type II, Sigma) was dissolved in 0.001 N HC1 at 1 mg/ml and further diluted 1/1000 in assay buffer (0.1 M Tris, pH 7.8 containing 0.1 M $CaCl_2$) before use. 0.75 µl of test compound in DMF (or DMF alone), 50 µl of assay buffer and 50 µl of enzyme were added to 96 wells plates, mixed and pre-incubated for 30 minutes at ambient temperature. Reaction was initiated by addition of 50 µl of 0.2 mM N-succinyl-Ala-Ala-Pro-Phe-p-nitroanilide (Sigma; 2 mM in DMSO diluted 1/10 in assay buffer before use). The increase in absorbance at 405 nm was monitored for 3 minutes with BIO-RAD model 3550 microplate reader.

Human Leukocyte Elastase Assay

Human leukocyte elastase (HLE) (CALBIOCHEM) was dissolved in saline at 1 mg/ml and further diluted 1/10 in assay buffer (0.2 M Tris, pH 8.0) before use.

0.75 µl of test compound in DMF (or DMF alone), 50 µl of assay buffer and 50 µl of enzyme were added to 96 well plate, mixed and pre-incubated for 30 minutes at ambient temperature. Reaction was initiated by addition of 50 µl of 2.5 mM methoxysuccinyl-Ala-Ala-Pro-Val-p-nitroanilide (Sigma; 25 mM in DMSO diluted 1/10 in assay buffer before use). The increase in absorbance at 405 nm was monitored for 3 min with BIO-RAD model 3550 microplate reader.

HPLC

condition A

Column: YMC-Pack ODS A-312 6.0×150mm

Eluent system:

Time(min)	0	20	30
MeCN(%)	5	100	100
10mMNaH_2PO_4aq.	95	0	0

Detection UV 254nm

Flow rate 1.0ml/min

condition B

Column: COSMOSIL 3C18 4.6×50mm

Eluent system:

Time(min)	0	5	15
MeCN(%)	30	90	90
10mMNaH_2PO_4aq.	70	10	10

Detection UV 254nm

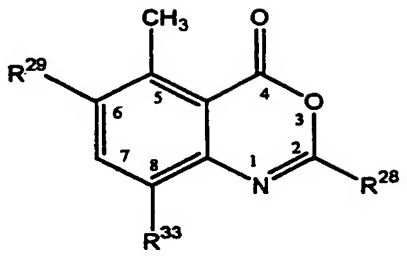
Flow rate 1.0ml/min.

COMPOUND	ENZYME IC50 (μM)	ANTIVIRUS EC50 (μM)	INHIBITION AT 50μM	
			HLE (%)	CHYMOTRYPSIN (%)
1	0.6	1.1	32	13
2	0.7	4.6	26	7
3	0.6	0.16	0	0
4	1.3	0.05	0	0
5	3.5	3.2	0	13.1
6	3.7	2.9	0	0
7	3.4	4.1	0	6.9
8	5	3.3	0	0
9	1.5	11.2	18.2	28.4
10	7.8	3.3	0	0
11	5.5	2.8	0	0
12	6.3	6.8	13.4	22.4
13	3.9	7.6	0	2.2
14	2	1.6	46.3	0
15	1.7	2.8	0	0
16	2.3	3.6	1.4	0
17	4.2	4.1	0	0
18	1.5	15.1	28.7	0
CC1	20.0	no data	no data	no data
CC2	3.2	7.5	101	101
CC3	3.2	48.9	100	100
CC4	no data	15.0	98	102
CC5	28.0	>50	100	98
CC6	11.8	>50	99	97

It will be apparent to those skilled in the art that various modifications and variations can be made in the compositions and methods of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

WHAT IS CLAIMED IS:

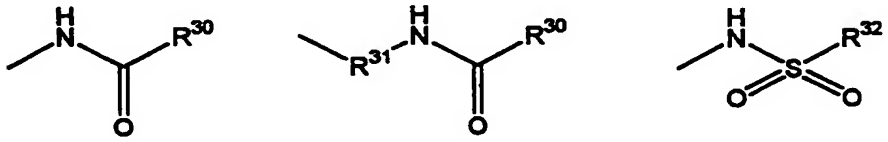
1. A compound of Formula II:



II

wherein R^{28} is selected from amino optionally substituted with two radicals selected from alkyl, aralkyl, heterocyclylalkyl, heterocyclyl, and aryl;

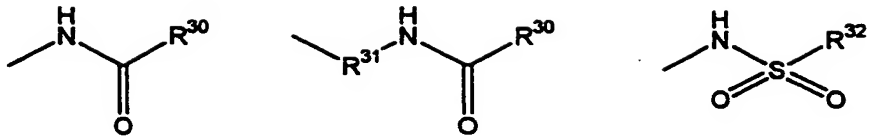
wherein R^{29} is selected from



wherein R^{30} is selected form alkyl, alkoxy, alkylamino, carboxyalkyl, alkoxyalkyl, alkylaminoalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aralkyl, aralkoxy, aryloxy, cycloalkyloxy, arylamino, aralkenyl, heterocyclylalkoxy, alkylaminoalkoxy, alkylaminoalkylamino, heterocyclylalkylamino, N-aryl-N-alkylamino, and N-aralkylamino; wherein R^{31} is alkyl; wherein R^{32} is selected from alkyl and aryl; and wherein R^{33} is selected from hydrido, halo and alkyl;

or a pharmaceutically-acceptable salt thereof.

2. Compound of claim 1 wherein R^{28} is selected from (a) amino optionally substituted with two radicals selected from lower alkyl, lower aralkyl, lower heterocyclylalkyl, heterocyclyl, and aryl, wherein R^{29} is selected from



wherein R^{30} is selected from lower alkyl, lower alkoxy, lower alkylamino, lower carboxyalkyl, lower alkoxyalkyl, lower alkylaminoalkyl, lower cycloalkyl, heterocyclyl, lower heterocyckylalkyl, lower heterocyclylalkoxy, lower aralkenyl, lower aralkyl, lower aralkoxy, phenyloxy, phenylamino, lower cycloalkyloxy, lower N-phenyl-N-alkylamino, lower alkylaminoalkoxy, lower alkylaminoalkylamino, lower heterocyclylalkylamino, and lower N-aralkylamino; wherein R^{31} is lower alkyl; wherein R^{32} is selected from lower alkyl and aryl; and

wherein R^{33} is selected from hydrido and lower alkyl; or a pharmaceutically-acceptable salt thereof.

3, Compound of claim 2 selected from compounds and their pharmaceutically-acceptable salts, of the group consisting of

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[methyl(phenylmethyl)-amino]-4H-3,1-benzoxazin-4-one;

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[methyl[(4-methoxyphenyl)-methyl]amino]-4H-3,1-benzoxazin-4-one;

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[1-(1,2,3,6-tetrahydro-pyridyl)]-4H-3,1-benzoxazin-4-one;

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[isopropyl(methyl)amino]-4H-3,1-benzoxazin-4-one;

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[(4-furoyl)piperazinyl]-4H-3,1-benzoxazin-4-one;

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[[(2-cyano)ethyl]-(cyclopropyl)amino]-4H-3,1-benzoxazin-4-one;

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[(4-thenoyl)piperazinyl]-4H-3,1-benzoxazin-4-one;

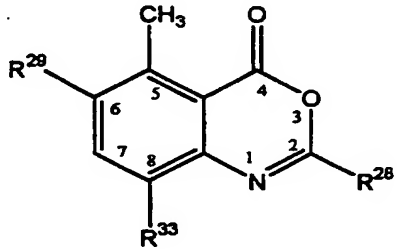
6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[(4-benzenesulfonyl)-piperazinyl]-4H-3,1-benzoxazin-4-one;
6-(benzoylamino)-5-methyl-2-[methyl(phenylmethyl)amino]-4H-3,1-benzoxazin-4-one;
6-[(Phenylmethoxyacetyl)amino]-5-methyl-2-(diisopropylamino)-4H-3,1-benzoxazin-4-one;
6-[(2,4,6-Trifluorobenzoyl)amino]-5-methyl-2(diisopropylamino)-4H-3,1-benzoxazin-4-one;
6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[[methyl(4-dimethylamino)-phenylmethyl]-amino]-4H-3,1-benzoxazin-4-one;
6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[methyl(2-pyridylmethyl)-amino]-4H-3,1-benzoxazin-4-one;
6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[methyl[2-(3-indolyl)ethyl]amino]-4H-3,1-benzoxazin-4-one;
6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-(4-morpholyl)-4H-3,1-benzoxazin-4-one;
6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[allyl(methyl)amino]-4H-3,1-benzoxazin-4-one;
6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-(1-decahydroquinolyl)-4H-3,1-benzoxazin-4-one; and
6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[4-(1-acetylpiperadinyl)]-4H-3,1-benzoxazin-4-one.

4. A pharmaceutical composition comprising a therapeutically-effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

5. A pharmaceutical composition comprising a therapeutically-effective amount of a compound of claim 2 and a pharmaceutically acceptable carrier or diluent.

6. A pharmaceutical composition comprising a therapeutically-effective amount of a compound of claim 3 and a pharmaceutically acceptable carrier or diluent.

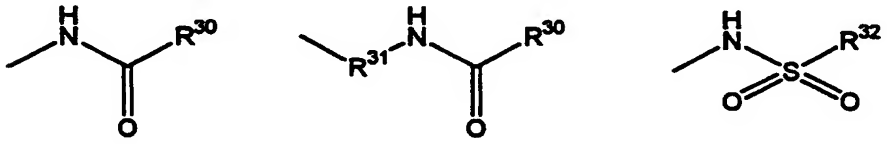
7. A method or therapeutic or prophylactic treatment of Herpes Simplex Virus in a subject, said method comprising treating said subject with an effective amount of a compound of Formula II:



II

wherein R^{28} is selected from (a) amino optionally substituted with two radicals selected from alkyl, aralkyl, heterocyclylalkyl, heterocyclyl, and aryl;

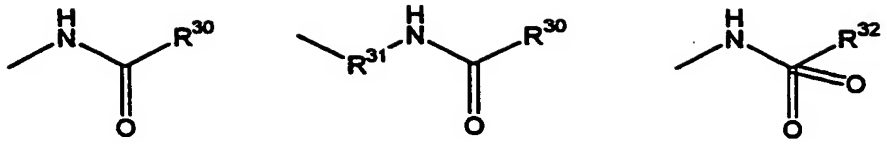
wherein R^{29} is selected from



wherein R^{30} is selected from alkyl, alkoxy, alkylamino, carboxyalkyl, alkoxyalkyl, alkylaminoalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aralkyl, aralkoxy, aryloxy, cycloalkyloxy, arylamino, aralkenyl, heterocyclylalkoxy, alkylaminoalkoxy, alkylaminoalkylamino, heterocyclylalkylamino, N-aryl-N-alkylamino, and N-aralkylamino; wherein R^{31} is alkyl; wherein R^{32} is selected from alkyl and aryl; and wherein R^{33} is selected from hydrido, halo and alkyl;

or a pharmaceutically-acceptable salt thereof.

8. The method of 7 wherein R^{28} is selected from (a) amino optionally substituted with two radicals selected from lower alkyl, lower aralkyl, lower heterocyclylalkyl, heterocyclyl, and aryl, wherein R^{29} is selected from



wherein R^{30} is selected from lower alkyl, lower alkoxy, lower alkylamino, lower carboxyalkyl, lower alkoxyalkyl, lower alkylaminoalkyl, lower cycloalkyl, heterocyclyl, lower heterocyckylalkyl, lower heterocyclylalkoxy, lower aralkenyl, lower aralkyl, lower aralkoxy, phenyloxy, phenylamino, lower cycloalkyloxy, lower N-phenyl-N-alkylamino, lower alkylaminoalkoxy, lower alkylaminoalkylamino, lower heterocyclylalkylamino, and lower N-aralkylamino; wherein R^{31} is lower alkyl; wherein R^{32} is selected from lower alkyl and aryl; and

wherein R^{33} is selected from hydrido and lower alkyl; or a pharmaceutically-acceptable salt thereof.

9. The method of claim 8 wherein the compound is selected from compounds and their pharmaceutically-acceptable salts, of the group consisting of
6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[methyl(phenylmethyl)-amino]-4H-3,1-benzoxazin-4-one;
6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[methyl[(4-methoxyphenyl)-methyl]amino]-4H-3,1-benzoxazin-4-one;
6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[1-(1,2,3,6-tetrahydro-pyridyl)]-4H-3,1-benzoxazin-4-one;
6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[isopropyl(methyl)amino]-4H-3,1-benzoxazin-4-one;
6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[(4-furoyl)piperazinyl]-4H-3,1-benzoxazin-4-one;
6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[[(2-cyano)ethyl]-(cyclopropyl)amino]-4H-3,1-benzoxazin-4-one;

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[(4-thenoyl)piperazinyl]-4H-3,1-benzoxazin-4-one;

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[(4-benzenesulfonyl)-piperazinyl]-4H-3,1-benzoxazin-4-one;

6-(benzoylamino)-5-methyl-2-[methyl(phenylmethyl)amino]-4H-3,1-benzoxazin-4-one;

6-[(Phenylmethoxyacetyl)amino]-5-methyl-2-(diisopropylamino)-4H-3,1-benzoxazin-4-one;

6-[(2,4,6-Trifluorobenzoyl)amino]-5-methyl-2(diisopropylamino)-4H-3,1-benzoxazin-4-one;

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[[methyl(4-dimethylamino)-phenylmethyl]-amino]-4H-3,1-benzoxazin-4-one;

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[methyl(2-pyridylmethyl)-amino]-4H-3,1-benzoxazin-4-one;

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[methyl[2-(3-indolyl)ethyl]amino]-4H-3,1-benzoxazin-4-one;

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-(4-morpholyl)-4H-3,1-benzoxazin-4-one;

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[allyl(methyl)amino]-4H-3,1-benzoxazin-4-one;

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-(1-decahydroquinolyl)-4H-3,1-benzoxazin-4-one; and

6-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-methyl-2-[4-(1-acetylpiperadinyl)]-4H-3,1-benzoxazin-4-one.

INTERNATIONAL SEARCH REPORT

International application N .

PCT/US00/18817

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/536; C07D 265/18

US CL : 514/230.5; 544/92

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/230.5; 544/92

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN/CAS: structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X, P	US 5,985,872 A (ABOOD et al.) 16 November 1999 (16.11.99), entire document.	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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